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EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/034,849	CALLEN ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *24-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 10/11/2003, is acknowledged.

2. Claims 1-28 are pending

3. Newly submitted claims 24-28 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 24-28 are drawn to a method for detecting or isolating a polymerase, making an antibody that binds to a polymerase, while claims 1-23 are drawn to an isolated or recombinant antibody that specifically binds to a polypeptide comprising SEQ ID NO: 2.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 30 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

4. Claims 24-28 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

5. Claims 1-23 are under examination as they read on an isolated or recombinant antibody that specifically binds to a polypeptide comprising SEQ ID NO: 2.

6. The following new grounds of rejection are necessitated by the amendment submitted 10/11/2003.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 16-19 and 22-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 16 is indefinite because it is unclear how the isolated or recombinant antibody would further comprise a detectable label. Further, Claim 16 has no antecedent basis in base claims 1 or 2, respectively, because claims 1 and 2 recite antibody per se, whereas further comprising a detectable label is recited in claim 16. It is unclear how an antibody would further comprise a detectable label.

B. Claim 18 is indefinite because it is unclear how the isolated or recombinant antibody would further comprise a solid support. Further, Claim 18 has no antecedent basis in base claims 1 or 2, respectively, because claims 1 and 2 recite antibody per se, whereas further comprising a solid support is recited in claim 18. It is unclear how an antibody would further comprise a solid support.

C. Claims 22-23 are indefinite because it is unclear how the isolated or recombinant antibody would further comprise a hybridoma cell or a transgenic mouse, respectively.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase "recombinant antibody" claimed in claims 1-23, the phrase "having at least 30 consecutive amino acids of a polypeptide (a) encoded by a nucleic acid comprising a sequence having at least 70% sequence identity to SEQ ID NO: 1 and encoding a polypeptide having polymerase activity or (b) having at lease 70% sequence identity to a sequence as set forth in SEQ ID NO:2" claimed in claim 2, the phrase "wherein the nucleic acid comprises a sequence having at least 70%,75% 80%/ 85%/90%/95%/97% sequence identity" claimed in claims 2-8, respectively, the phrase "*further* comprising a hybridoma cell" claimed in claim 22, and the phrase "*further* comprising a transgenic mouse" claimed in claim 23, represent a departure from the specification and the claims as originally filed.

Applicant's amendment filed 10/11/2003 points to the specification at pages 55-56 for support for the newly added limitations "recombinant antibody" claimed in claims 1-29, "having at least 30 consecutive amino acids of a polypeptide (a) encoded by a nucleic acid comprising a sequence having at least 70% sequence identity to SEQ ID NO: 1 and encoding a polypeptide having polymerase activity or (b) having at lease 70% sequence identity to a sequence as set forth in SEQ ID NO:2" claimed in claim 2, "wherein the nucleic acid comprises a sequence having at least 80%/ 85%/90%/95%/97% sequence identity" claimed in claims 4-8, respectively, and the phrase "wherein the polypeptide has at least 85% 90%, 95%, or 97% sequence identity" claimed in claims 11-14, "*further* comprising a transgenic mouse" and "*further* comprising a transgenic mouse". However, the specification does not provide a clear support of for such recitations. It is noticed that the specification provides support for only humanized antibody as a recombinant antibody. Further, the specification provides support of the % homology of the full length alone and the 30 consecutive amino acids alone, however no support for the combination of both the % homology and the specific fragments is provided of SEQ ID NO:1. The instant claims now recite limitations which were not clearly disclosed in the specification and recited in the claims as originally filed.

11. In view of the amendment filed on 10/11/2003, only the following rejections remained.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-8, 10-14 and 16-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody which specifically binds SEQ ID NO: 2 for screening assay, does not provide enablement for an antibody that specifically binds to a polypeptide (a) encoded by a nucleic acid comprising a sequence having at least 70%, 75%, 80%, 85%, 90% 95% or 97% sequence identity to SEO ID NO:1 and encoding a polypeptide having polymerase activity, or (b) having polymerase activity and at least 75%, 85%, 90%, 95%, 97% sequence identity to a sequence as set forth in SEQ ID NO:2 in claims 1 and 3-15, an antibody that specifically binds to a polypeptide having at least 30 consecutive amino acids of a polypeptide (a) encoded by a nucleic acid comprising a sequence having at least 70%, 75%, 80%, 85%, 90% 95% or 97% sequence identity to SEO ID NO: 1 and encoding a polypeptide having polvmerase activity. or (b) having at least 75%, 85%, 90%, 95%, 97% sequence identity to a sequence as set forth in SEO ID NO:2 in claims 2-15. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claim for the same reasons set forth in the previous Office Action mailed 06/16/2003.

Applicant's arguments, filed 10/11/2003, have been fully considered, but have not been found convincing.

Applicant is relying upon certain biological activities and the disclosure of a single species to support an entire genus. The claims as written encompass a broad genus of polypeptides with an unlimited number of possibilities with regard to the length of the polypeptide sequence. Further, the enablement issues of making the protein still remain because the specification does not teach and provide sufficient guidance as to which amino acid of SEQ ID NO:4 would have been altered such that the resultant polypeptide would have retained the functional activity of the alpha-glactosidase. Therefore, absent the ability to predict which of these peptides would function as claimed, and given the lack of data on regions critical for activity, for one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.

Applicant asserts that the specification enabled the skilled artisan at the time of the invention to identify and make and use a genus of polymerase activity to practice the claimed invention, e.g., to make and use antibodies that bind to polymerase activity. Further Applicant draws the Examiner's attention to Dr. Jay Short declaration that the state of the art at the time of the invention and the level of skill of the person of ordinary skill in the art, e.g., in screening enzymes, and nucleic acids encoding enzymes, for polymerase activity, was very high.

This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. Further, the claims fail to meet the enablement requirement for the "how to make and use" prongs of the U.S.C 112, 1st paragraph, in order to satisfy the U.S.C 112, 1st paragraph, the specification has to teach how to make and/or use the invention, not how to screen to identify the invention. Until the time when the at least 75%-100 sequence identity polypeptides are found, then one skill in the art can make them then produce antibodies to them.

Applicant further submits that Dr. Short declared that using the teaching of the specification, one skilled in the art could have selected routine methods known in the art at the time of the invention to express variants and fragments of nucleic acids encoding the exemplary enzyme of the invention and screen them for expression of polypeptides and peptides having polymerase activity. Further, Dr. Short declared one skill in the art could have selected routine methods known in the art at the time of the invention, including those described in the instant specification, to make and screen for immunogenic peptides, e.g. fragments of polypeptides, comprising polypeptides and peptides having a percent sequence identity to SEQ ID NO: 2, or active fragments thereof. Dr, Short declared that it would not have required any knowledge or guidance as to which are the specific structural elements results that correlated with polymerase activity to create variants or fragments of exemplary nucleic acids and test them for the expression of polypeptides having polymerase activity.

However, there is insufficient guidance to direct a person of skill in the art to select particular sequences or sequence lengths as essential for polymerase activity. Without detailed direction as to which amino acid sequences are essential to the function of the polypeptide, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of amino acid sequences encompassed by the instant claims would share the function of polymerase activity of the polypeptide of SEQ ID NO:2, other than the amino acid of SEQ ID NO:2.

14. The declaration by Dr. Short under 37 CFR 1.132 filed 10/11/2003 is insufficient to overcome the rejection of claims 1-8, 10-14 and 16-23 based upon 35 U.S.C. 112, first paragraph as set forth in the last Office action because the specification has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Due to the large quantity of experimentation necessary to obtain "75% sequence identity to at least 30 consecutive amino acids of any sequence of SEQ ID NO:2", to generate the infinite number of derivatives recited in the claims, and to determine the specific activity of the infinite variants, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the state of the prior art which establishes that biological activity cannot be predicted based on structural similarity, and the breadth of the claims which embrace a broad class of structural variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

15. Claims 1-8, 10-14 and 16-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 6/16/2003.

Applicant's arguments, filed 10/11/2003, have been fully considered, but have not been found convincing.

Applicant is in possession of an antibody that specifically binds SEQ ID NO: 2.

Applicant is not in possession of an antibody that specifically binds to a polypeptide (a) encoded by a nucleic acid comprising a sequence having at least 70%, 75%, 80%, 85%, 90% 95% or 97% sequence identity to SEO ID NO:1 and encoding a polypeptide having polymerase activity, or (b) having polymerase activity and at least 75%, 85%, 90%, 95%, 97% sequence identity to a sequence as set forth in SEQ ID NO:2 in claims 1 and 3-15, an antibody that specifically binds to a polypeptide having at least 30 consecutive amino acids of a polypeptide (a) encoded by a nucleic acid comprising a sequence having at least 70%, 75%, 80%, 85%, 90% 95% or 97% sequence identity to SEO ID NO: 1 and encoding a polypeptide having polymerase activity. or (b) having at least 75%, 85%, 90%, 95%, 97% sequence identity to a sequence as set forth in SEO ID NO:2 in claims 2-15.

Applicant submits that only structurally and functionally related enzymes are specifically bound by the antibodies of the invention. The enzymes are specifically bound by the antibodies of the claimed invention are described by structure (the exemplary sequence), a physico-chemical property (percent sequence identity) and function (polymerase activity). A11 enzymes are specifically bound by the antibodies of the claimed invention must have a percent sequence identity to an exemplary polymerase coding sequence. Applicants respectfully submit that describing a genus of polypeptides (and, the antibodies that specifically bind to them) in terms of physico-chemical properties (e.g., sequence identity or hybridization conditions) and function (e.g., encoding polypeptides having polymerase activity) satisfies the written description requirement of section 112, first paragraph. Applicant argues for an adequate written description to be achieved (1) there is no bright line rule that a single species is insufficient to put one of skill in the art in possession of the attributes and features of all species with a genus. Applicant points to the USPTO guidelines concerining compliance with the written description requirement, (2) a description of a genus of polynucleotides in terms of its physcio-chemical properties, e.g.a % sequence identity, to a single exemplary species, and (3) a common function.

However, the Examiner notes that the claimed invention which is drawn to a genus may be adequately described if there is a (1) sufficient description of a representative number of species, or (2) by disclosure of relevant, identifying characteristics sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize

applicant was in possession of the claimed invention. To satisfy the disclosure of a "representative number of species" will depend on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. "Relevant, identifying characteristics" include structure or other physical and /or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics sufficient to show the applicant was in possession of the claimed genus. (see Revised Guidelines for the Examination of Patent Applications Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No.4, pages 1099-1111, Friday January 5, 2001).

In the instant case, however, there is no described or art-recognized correlation or relationship between the structure of the invention SEQ ID NO:2, the and it's polymerase activity function, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of variants, wherein the variant has at least 75% sequence identity to at least 10 consecutive amino acids of any sequence of SEQ ID NO: 2, which retain the features essential to the instant invention.

While applicant points to Example 14 of the Guidelines is analogous to the genus of peptides and polypeptides of the invention at hand. Contrary to Applicant assertions the Example 14 is drawn to variants that are at least 95% identical to a full length protein with the specific enzymatic activity. The instant claims are drawn to any protein comprising any fragment that is 75% sequence identity to at least 30 consecutive amino acids of a sequence of SEQ ID NO:2 and has polymerase activity.

Applicant refers to recently issued claims directed to genuses of polynucleotides based on sequence identity (and stringent hybridization) to an exemplary nucleic acid, see, e.g., recently issued claims directed to, e.g., 72.5% sequence identity, as in USPN 6,593,514, 75% sequence identity, as in USPN 6,586,215, 80% sequence identity, as in USPN 6,596,926; 85% sequence identity, ms in USPN 6,590,141 and USPN 6,586,179; 86% sequence identity, as in USPN 6,583,337; 90% sequence identity (and 'stringent hybridization'), as in USPN 6,541,684 (see Exhibit B).

It is well settled that whether similar claims have been allowed to others is immaterial. See In re Giolito, 530 F.2d 397, 188 USPQ 645 (CCPA 1976) and Ex parte Balzarini 21 USPQ2d 1892, 1897 (BPAI 1991). Moreover, as stated In re Borkowski, 505 F2d 713,718,184 USPQ29,33 (CCPA 1974), "The Patent Office must have the flexibility to reconsider and correct prior decisions that may find to have been in error". In a similar context, the court in Fessenden v.Coe, 38 USPQ 516,521 (CADC 1938) stated that '[t]wo wrongs cannot make a right."

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 1-15 and 20-22 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 5,491,086 (IDS Ref. # AG), as is evidenced by Bost et al. and Bendayan.

The `086 patent teaches antisera or monoclonal antibodies that binds to peptides designed from Pyrodictium DNA polymerase (see column 13, lines 52-56 in particular), wherein Pyrodictium DNA polymerase has 71% identity to claimed SEQ ID NO:2 (see sequence alignment in particular). The patented Pyrodictium DNA polymerase having a fragment of at least 30 consecutive amino acids (aa 628-657) that are 96% identical to fragments of claimed polypeptide of SEQ ID NO: 2. The fragment is encompassed within 803 amino acid sequence and is included because "having" in the instant claims opens the claims up to include additional unrecited elements even in large amounts. Further, antibodies "cross-react" with antigens with homolgous amino acid residues. Further, the patented Pyrodictium DNA polymerase is considered substantially identical to SEQ ID NO: 2. Although the `086 patent does not teach specific amino acid sequence of SEQ ID NO:2, binding to "SEQ ID NO:2" is considered an inherent property of the reference antibody.

As is evidenced by Bost *et al* that an antibody "cross-reacts", i.e. binds to more than one protein sequence, which mean that "specifically bind" with both proteins. Bost et al (Immuno. Invest. 1988 ;17:577-586) describe antibodies which "cross-react" with IL-2 and HIV envelope protein, but establish that the binding of each protein is due to the presence of a homologous sequence in each protein in which 4-6 residues were identical (see entire document, especially the Abstract and Discussion).

Similarly, Bendayan (J. Histochem. Cytochem. 1995, 43:881-886) characterizes the specific reactivity of a monoclonal antibody produced to human proinsulin, and shows that although the antibody is highly specific, it is nevertheless able to bind to not only human proinsulin, but to proinsulin from other species and even a distinct protein, glucagons, based upon conservation of an Arg-Arg dipeptide sequence in each of these molecules (see entire document). Bendayan concludes that "an antibody directed against such a sequence, although still yielding specific labeling, could reveal different molecules not related to the original antigen" (page 886, last paragraph in particular).

Claim 22 is included because the Examiner interprets the claim as antibody produced by a hybridoma cell. Thus, it is well known in the art that monoclonal antibodies are produced by a hybridoma cell.

Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody does not bind to the SEQ ID NO:2 recited in the claims. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

Applicant's arguments, filed 10/11/2003, have been fully considered, but have not been found convincing.

Applicant asserts that claim 1 is drawn to antibodies that specifically bind to a polypeptide (a) encoded by a nucleic acid comprising a sequence having at least 70% sequence identity to SEQ ID NO:1 and encoding a polypeptide having polymerase activity, or (b) having polymerase activity and at least 75% sequence identity to a sequence as set forth in SEQ ID NO:2. Thus Gelfand, et al., is not a single prior source that contains each and every limitation of the invention as set forth in claim 1. Further, applicant asserts that, claim 2 is drawn to antibodies that specifically bind to a polypeptide having at least 30 consecutive amino acids of a polypeptide (a) encoded by a nucleic acid comprising a sequence having at least 70% sequence identity to SEQ ID NO:1 and encoding a polypeptide having polymerase activity, or (b) having at least 80% sequence identity to a sequence as set forth in SEQ ID NO:2. Applicant argues that Gelfand, et al., is not a single prior source that contains each and every limitation of the invention as set forth in claim 2. Applicants aver that because Gelfand, et al., is not a single prior source that contains each and every limitation of the claimed invention, the rejection under section 102(b) can be properly withdrawn. Finally Applicant argues regarding "cross-reacting antibodies" that the claimed invention is drawn to antibodies that specifically bind to a polypeptide of the invention, i.e., antibodies that will not bind to non-claimed polymerases, e.g., the polymerase taught by Gelfand, et al. Accordingly, "cross-reacting antibodies" are outside of the scope of the instant claimed invention.

Contrary to applicant assertion Gelfand *et al* teach antibodies that bind the same or nearly the same antigenic determinants/epitopes which meet the claimed antibody specificities. Further, given the high sequence identity/homology between the referenced/claimed polypeptides; the referenced antibodies would have the inherent property of binding SEQ ID NO:2 or a polypeptide encoded by SEQ ID NO:1 in the absence of objective evidence to the contrary.

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 1-15 and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uemori et al (J. Bacteriol. 177:2164-2177, 1995), in view of Alisa Campbell (General properties and applications of monoclonal antibodies, Elsevier Science Publishers, 1984, section 1.1).

Uemori *et al* teach the polypeptide that is substantially identical that is 71% of claimed SEQ ID NO: 2 (see sequence alignment, Fig 3 page 2167 in particular). Uemori *et al* further teach the highly conserved sequence VIYGDTD (corresponding to amino acids 574-580 of SEQ ID NO:2) which is responsible for DNA synthesis and is important for the catalysis of DNA polymerization and dNTP binding (see Fig 1, page 2165 and page 2169 under Results and Discussion in particular). Further, the Uemori *et al* referenced polypeptide having a fragment of at least 30 consecutive amino acids that are 96% identical to fragment of claimed polypeptide of SEQ ID NO: 2, (see sequence alignment in particular). Finally, Uemori *et al* teach that DNA polymerase is one of the most important enzymes for living cells (see column 1, line 45-48 in particular).

The claimed invention differs from the reference teachings only by the recitation of an antibody which specifically binds to a polypeptide having encoded by a nucleic acid comprising a sequence having at least 70%, 75%, 80%, 85%, 90%, 95%, 97% or 100% sequence identity to SEQ D NO:1 and encoding a polypeptide having polymerase activity, or (b) having polymerase activity and at least 75%, 85%, 90%, 97% sequence identity to a sequence as set forth in SEQ ID NO:2 in claims 1 and 3-15; an antibody that specifically binds to a polypeptide having at least 30 consecutive amino acids of a polypeptide (a) encoded by a nucleic acid comprising a sequence having at least 70%, 75%, 80%, 85%, 90%, 95%, 97% or 100% sequence identity to SEQ ID NO:1 and encoding a polypeptide having polymerase activity, or (a) having at least 75%, 85%, 90%, 97% sequence identity to a sequence as set forth in SEQ ID NO:2 of SEQ ID NO: 2 and sequences substantially identical thereto in claims 2-15, wherein the antibody is a monoclonal in claim 21.

Campbell teaches that it is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (see page 3 figure 11.1 in particular). One field of research in which monoclonal antibodies may prove of particular value is in the study of chromosomal proteins. The search for those chromosomal proteins which are responsible for determining cell phenotype has been particularly long and comparatively fruitless and monoclonal antibodies are ideal tools for the dissection of the complex mixture of proteins. As hybridoma production becomes a more routine laboratory technique (see page 29 and 30 under Basic research in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an antibody as taught by Campbell against the polypeptide of the DNA polymerase taught by the Uemori *et al* reference.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because it was customary at the time the invention was made to make monoclonals against

any new macromolecule as taught by Campbell, wherein the such DNA polymerase is one of the most important enzymes for living cells, and further, the DNA polymerase contains highly conserved sequence which is responsible for DNA synthesis and is important for the catalysis of DNA polymerization and dNTP binding as taught by the Uemori *et al* reference.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 10/11/2003, have been fully considered, but have not been found convincing.

Applicants submit that claim 1 as amended is drawn to antibodies that specifically bind to a polypeptide (a) encoded by a nucleic acid comprising a sequence having at least 70% sequence identity to SEQ ID NO:1 and encoding a polypeptide having polymerase activity, or (b) having polymerase activity and at least 75% sequence identity to a sequence as set forth in SEQ ID NO:2. Applicant further argues that Alisa Campbell does not teach a polymerase of the claimed invention. Applicant asserts that claim 2, as amended, is drawn to antibodies that specifically bind to a polypeptide having at least 30 consecutive amino acids of a polypeptide (a) encoded by a nucleic acid comprising a sequence having at least 70% sequence identity to SEQ ID NO:1 and encoding a polypeptide having polymerase activity, or (b) having at least 75% sequence identity to a sequence as set forth in SEQ ID NO:2. Further Alisa Campbell does not teach a polymerase of the claimed invention. Applicants aver that because Uemori, et al. in combination with Alisa Campbell do not teach a polymerase of the claimed invention, the rejection under section 103(a) can be properly withdrawn.

However, antibodies that bind the same or nearly the same epitopes would meet the claimed antibody specificities. Furthermore, the issue is the obviousness for one ordinary skill in the art at the time of the invention was made to use the same polymerase/fragments taught by Uemori et al to make monoclonal antibodies as taught by Campbell. Further, given the high sequence identity/homology between the referenced/claimed polypeptides; the referenced antibodies would have the inherent property of binding SEQ ID NO:2 or fragments thereof in the absence of objective evidence to the contrary.

20. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Uemori et al (J. Bacteriol. 177:2164-2177, 1995), in view of Alisa Campbell (General properties and applications of monoclonal antibodies, Elsevier Science Publishers, 1984, section 1.1) as applied to claims 1-15 and 21 above, and in view of U.S. Patent No. 6,057,098.

The teachings of Uemori et al and Campbell references have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a polyclonal antibody in claim 20.

The `098 patent teaches methods of producing polyclonal polypeptides having specific affinity for a target. The `098 patent further teaches the use of polyclonals has a number of advantages with respect to monoclonals. By binding to multiple sites on a target, polyclonal antibodies can generate a stronger signal (for diagnostics) or greater blocking/inhibition/cytotoxicity (for therapeutics) than a monoclonal that binds to a single site. Further, a polyclonal preparation can bind to numerous variants of a prototypical target sequence (e.g., allelic variants, species variants, strain variants, drug-induced escape variants) whereas a monoclonal antibody may bind only to the prototypical sequence or a narrower range of variants thereto.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce polyclonal antibody using the method taught by `098 patent with the polypeptide taught by the Uemori et al.

One ordinary skill in the art at the time the invention was made would have been motivated to make polyclonal antibody to the various polypeptides of SEQ ID NO: 2 because the use of polyclonals has a number of advantages with respect to monoclonals. By binding to multiple sites on a target, polyclonal antibodies can generate a stronger signal (for diagnostics) or greater blocking/inhibition/cytotoxicity (for therapeutics) than a monoclonal that binds to a single site. Further, a polyclonal preparation can bind to numerous variants of a prototypical target sequence (e.g., allelic variants, species variants, strain variants, drug-induced escape variants) whereas a monoclonal antibody may bind only to the prototypical sequence or a narrower range of variants thereto as taught by the `098 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

21. Claims 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uemori et al (J. Bacteriol. 177:2164-2177, 1995), in view of Alisa Campbell (General properties and applications of monoclonal antibodies, Elsevier Science Publishers, 1984, section 1.1) as applied to claims 1-15 and 21-22 above, and in view of U.S. Patent No. 5,514,599.

The teachings of Uemori et al and Campbell references have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a detectable lablel in claim 16, wherein the detectable label comprises an enzyme lable a radioisotope, in claim 17, a solid support in claim 18, wherein the solid support comprises a bead or a column matrix in claim 19.

The `599 patent teaches antibodies that can be used for the preparation of immunoassays. In such immunoassays, the antibodies can be immobilized on a solid phase. Processes for the immobilization of antibodies on solid phases such as synthetic or natural polymers such as polystyrene, polypropylene, PVC or latex in various geometrical embodiments such as tubes, beads or microtiter plates are known to those skilled in the art. The `599 patent further teaches labeled antibodies for detection. Labeling is normally carried out via a radioactive, chemiluminescent or enzymatic label. Finally, the `599 patent teaches it is advantageous to label the antibodies for the preparation of a multi species immunoassay and thus design an RIA (radioimmunoassay), CIA/LIA ((chemi)-luminescence immunoassay) or EIA (enzyme immunoassay) by processes known from the literature (col. 4, lines 36-64 in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to further add a detectable label or a solid support to the antibody taught by the Uemori et al in view of Campbell, such labels are an enzymatic label or a radioisotope, and such solid supports are beads or column matrix taught by the `599 patent.

One ordinary skill in the art at the time the invention was made would have been motivated to do so because labeled antibody can be used for the preparation of a multi species immunoassay and thus design an RIA, CIA/LIA or EIA as taught by the `599 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

22. Claims 1-2 and 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,491,086 (IDS Ref. # AG), as is evidenced by Bost et al. and Bendayan and in view of U.S. Patent No. 5,514,599.

The teachings of the `086 patent and Bost et al. and Bendayan evidentiary references have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a detectable lablel in claim 16, wherein the detectable label comprises an enzyme lable a radioisotope, in claim 17, a solid support in claim 18, wherein the solid support comprises a bead or a column matrix in claim 19.

The `599 patent teaches antibodies that can be used for the preparation of immunoassays. In such immunoassays, the antibodies can be immobilized on a solid phase. Processes for the immobilization of antibodies on solid phases such as synthetic or natural polymers such as polystyrene, polypropylene, PVC or latex in various geometrical embodiments such as tubes, beads or microtiter plates are known to those skilled in the art. The `599 patent further teaches

labeled antibodies for detection. Labeling is normally carried out via a radioactive, chemiluminescent or enzymatic label. Finally, the `599 patent teaches it is advantageous to label the antibodies for the preparation of a multi species immunoassay and thus design an RIA (radioimmunoassay), CIA/LIA ((chemi)-luminescence immunoassay) or EIA (enzyme immunoassay) by processes known from the literature (col. 4, lines 36-64 in particular)..

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to further add a detectable label or a solid support to the antibody taught by the `086 patent, such labels are an enzymatic label or a radioisotope, and such solid supports are beads or column matrix taught by the `599 patent.

One ordinary skill in the art at the time the invention was made would have been motivated to do so because labeled antibody can be used for the preparation of a multi species immunoassay and thus design an RIA, CIA/LIA or EIA as taught by the `599 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

23. Claims 1 and 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,491,086 (IDS Ref. # AG), as is evidenced by Bost et al. and Bendayan and in view of U.S. Patent No. 5,770,429.

The teachings of the `086 patent and Bost et al. and Bendayan evidentiary references have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a transgenic mouse.

The `429 patent teaches a transgenic mice which have inactivated endogenous mouse heavy chain loci which retain intact heavy chain constant region genes, and which have a human heavy chain transgene capable of trans-switching, and optionally also have a human light chain transgene, optionally with one or more inactivated endogenous mouse light chain loci. The `42 patent further teaches that such mice can advantageously produce B cells capable of alternatively expressing antibodies comprising fully human heavy chains and antibodies comprising chimeric (human variable/mouse constant) heavy chains, by trans-switching. The serum of said mice would contain antibodies comprising fully human heavy chains and antibodies comprising chimeric (human variable/mouse constant) heavy chains, preferably in combination with fully human light chains. Hybridomas can be generated from the B cells of said mice (see col. 43, lines 1-13 in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to generate the antibody taught by the `086 patent using a transgenic mice taught by the `429 patent.

One ordinary skill in the art at the time the invention was made would have been motivated to do so because such mice can advantageously produce B cells capable of alternatively expressing antibodies comprising fully human heavy chains and antibodies comprising chimeric (human variable/mouse constant) heavy chains, by trans-switching as taught by the `429 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

24. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Uemori et al (J. Bacteriol. 177:2164-2177, 1995), in view of Alisa Campbell (General properties and applications of monoclonal antibodies, Elsevier Science Publishers, 1984, section 1.1) as applied to claims 1-15 and 21-22 above, and in view of U.S. Patent No. 5,770,429.

The teachings of Uemori et al and Campbell references have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a transgenic mouse.

The `429 patent teaches a transgenic mice which have inactivated endogenous mouse heavy chain loci which retain intact heavy chain constant region genes, and which have a human heavy chain transgene capable of trans-switching, and optionally also have a human light chain transgene, optionally with one or more inactivated endogenous mouse light chain loci. The `42 patent further teaches that such mice can advantageously produce B cells capable of alternatively expressing antibodies comprising fully human heavy chains and antibodies comprising chimeric (human variable/mouse constant) heavy chains, by trans-switching. The serum of said mice would contain antibodies comprising fully human heavy chains and antibodies comprising chimeric (human variable/mouse constant) heavy chains, preferably in combination with fully human light chains. Hybridomas can be generated from the B cells of said mice (see col. 43, lines 1-13 in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to generate the antibody taught by Uemori et al in view of Campbell using a transgenic mice taught by the `429 patent.

One ordinary skill in the art at the time the invention was made would have been motivated to do so because such mice can advantageously produce B cells capable of alternatively expressing antibodies comprising fully human heavy chains and antibodies comprising chimeric (human variable/mouse constant) heavy chains, by trans-switching as taught by the `429 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

25. No claim is allowed.

26. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9307.

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Technology Center 1600
December 29, 2003

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